IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	TENDO et al.
Confirmation No.:	5815
Group Art Unit:	1625
Serial No.:	10/553,946
Examiner:	DAVID E GALLIS
Filed:	October 21, 2005
For:	SALT OF (2S,3S)-3-[[(1S)-1-ISOBUTOXYMETHYL-3-METHYLBUTYL]CARBAMOYL]OXIRANE-2-CARBOXYLIC ACID

DECLARATION PURSUANT TO RULE 132

Honorable Commissioner of Patents and Trademarks
Washington, D.C.

I, Toshihiro TAKAHASHI, one of the above-named applicants, declare and state that:

I hereby submit the below-described materials to show differences between the product (Example 48) of Nomura et al. and the product (Example 9) of the present invention.

1. Summary

I compared the obtained Samples 1 and 2 according to the following methods.

(1) IR spectra

The following IR spectra are submitted.

IR spectrum 1 (Fig. 1) which was obtained on February 26, 1998 (its characteristic peaks are described in Example 48 of Nomura et al.)

IR spectrum 2 (Fig. 2) which was obtained on October 17, 2002 (its characteristic peaks are described in Example 9 of the present invention)

IR spectrum 3 (Fig. 3) which has been newly obtained for Sample 1

IR spectrum 4 (Fig. 4) which has been newly obtained for Sample 2

IR spectrum 5 (Fig. 5) which shows the IR spectra 3 and 4 in one sheet for comparison

(2) Microscopic pictures

The following microscopic pictures are submitted.

Polarizing microscopic pictures 1-4 (Figs. 6-9) which have been newly obtained for Sample 1

Polarizing microscopic pictures 5-8 (Figs. 10-13) which have been newly obtained for Sample 2

Electron microscopic pictures 1 and 2 (Figs. 14 and 15) which obtained on July 6, 2004 for Sample 2

(3) Powdery X-ray diffraction data (PXRD)

The following powder X-ray diffraction data (PXRD) are submitted.

PXRD 1 (Fig. 16) which was obtained on July 25, 2001 for Sample 1

PXRD 2 (Fig. 17) which was obtained on December 17, 2001 for Sample 2

(4) Analysis of Sample 2 using DSC (heating elevation rate: 2°C/minute)

The DSC data (heating elevation rate: 2°C/minute) of the following Entries C to H are submitted. The term "Entries" means lot numbers, which has been prepared under slightly varying drying conditions.

Entries A and B were obtained as Example 9 of the present invention before filing the subject application.

Entries C to H were obtained for Sample 2 after filing the subject application.

The results are set forth in Table I.

(5) Analyses of Samples 1 and 2 using DSC (heating elevation rate: 2°C/minute)

The DSC data (heating elevation rate: 2°C/minute) of the following Entries 1 to 4 are submitted. The term "Entries" means lot numbers, which have been prepared under slightly varying drying conditions.

Entries 1 to 3 have been newly prepared for Sample 1.

Entry 4 was prepared for Sample 2 after filing the subject application.

The results are set forth in Table II.

DSC chart 1 (Fig. 18) which has been newly obtained for Entry 1 (for Sample 1)

DSC chart 2 (Fig. 19) which has been newly obtained for Entry 2 (for Sample 1)

DSC chart 3 (Fig. 20) which has been newly obtained for Entry 3 (for Sample 1)

DSC chart 4 (Fig. 21) which has been newly obtained for Entry 4 (for Sample 2)

(6) Analyses of Samples 1 and 2 using DSC (heating elevation rate: 5°C/minute)

The DSC data (heating elevation rate: 5°C/minute) of the Entries 1 to 4 shown above are submitted.

The results are set forth in Table III.

2. Preparation of sodium salts employed for observation

I prepared sodium salts as Samples 1 and 2. Sample 1 corresponds to the Na salt given in Table 1 of our specification on page 23, lines 8-9 (obtained according to the conventional process), that is the process (Example 48) of Nomura et al. Sample 2 corresponds to the Na salt given in Table 1 of our specification on page 23, lines 14-15 (obtained in Example 9), that is according to our invention.

Details of the preparation procedures are described below.

(1) Sample 1

(2S,3S)-3-[[(1S)-1-isobutoxymethyl-3-methylbutyl]carbamoyl]oxirane-2-carboxylic acid (46.13 g, 160.5 mmol) was dissolved in ethyl acetate (250 mL) and combined with an aqueous solution (250 mL) of sodium hydrogen carbonate (12.81 g, 152.5 mmol). The mixture was violently shaken in a separating funnel. The aqueous portion was taken out and placed under reduced pressure in a bath maintained at a temperature of lower than 35°C to distill off the solvent, to give sodium (2S,3S)-3-[[(1S)-1-isobutoxymethyl-3-methylbutyl]carbamoyl]oxirane-2-carboxylate. There was obtained a white mainly amorphous product.

(2) Sample 2

The sodium (2S,3S)-3-[[(1S)-1-isobutoxymethyl-3-methylbutyl]carbamoyl]oxirane-2-carboxylate (25.18 g) prepared in Example 8 given in our specification on pages 17-18 was dissolved in methanol (85 mL) at 50°C, and ethyl acetate (100 mL) was dropped while the temperature was kept. While the temperature was still kept, a seed crystal was placed in the solution, the solution was stirred for 1 hour, and ethyl acetate (150 mL) was again dropped. While the temperature was still kept, ethyl acetate (100 mL) was further dropped and furthermore ethyl acetate (75 mL) was dropped, and then the solution was stirred for 1 hour. While gradually cooled to room temperature, the solution was stirred overnight. The precipitated crystalline product was collected by filtration, washed with three portions of a mixture of ethyl acetate/methanol (5/1, 40 mL, 25 mL, 25 mL) in a stream of nitrogen gas. Before completely dried in air, the crystalline product was dried under reduced pressure at

40°C overnight to obtain sodium (2S,3S)-3-[[(1S)-1-isobutoxymethyl-3-methylbutyl]carbamoyl]oxirane-2-carboxylate in white crystalline needles.

3. Analyses of the submitted experimental data

(1) IR spectra

There seems to be a significant difference between IR spectrum 1 (Fig. 1) and IR spectrum 2 (Fig. 2).

However, the difference is understood to have been caused by differences in the instrument for measurement and experimental conditions.

IR spectrum 1 (Nomura et al.) was measured using JIR-6500 (JEOL), which is a Fourier transformation infrared spectrophotometer (FT-IR) type. The wavenumbers of peaks were automatically read and printed out in the chart. The printed wavenumbers are accurate to several decimal places.

On the other hand, the IR spectrum 2 (Present invention) was measured using Type 260-50 (Hitachi), which is a dispersion type (not the FT-IR type). The wavenumbers of peaks were visually read. It is impossible to read the wavenumbers accurately at the level of less than 10 cm^{-1}, because the scale is 20 cm^{-1} (within the area of low wavenumbers) or 50 cm^{-1} (within the area of high wavenumbers).

Therefore, I have newly obtained the IR spectrum of Sample 1 (Nomura et al.) and that of Sample 2 (present invention) using the same instrument under the same experimental conditions.

IR spectrum 3 (Fig. 3) and IR spectrum 4 (Fig. 4) have been obtained using Fourier Transform Infrared Spectroscopy FT-720 (Horiba) under the same conditions.

The IR spectra 3 and 4 are compared in one sheet (IR spectrum 5, Fig. 5). Apparently, there is no significant difference in the IR spectrum between the product (Exam-

ple 48) of Nomura et al. and the product (Example 9) of the present invention.

Accordingly, it has been confirmed that the IR data are not characteristic feature for the present invention.

(2) Microscopic pictures

As is shown in polarizing microscopic pictures 1-4 (Figs. 6-9), Sample 1 is in the form of mainly amorphous product.

As is shown in polarizing microscopic pictures 5-8 (Figs. 10-13), Sample 2 is in the form of crystalline product.

As is also shown in electron microscopic pictures 1 and 2 (Figs. 14 and 15), Sample 2 is in the form of crystalline product.

(3) Powder X-ray diffraction data (PXRD)

As is shown in PXRD 1 for Sample 1 (Fig. 16), there are no sharp diffraction peaks. The whole diffraction peaks are broad. These broad peaks indicate that Sample 1 is mainly amorphous.

As is shown in PXRD 2 for Sample 2 (Fig. 17), there are sharp diffraction peaks at the diffraction angles (2θ) of 12° and 17°, which indicate that Sample 2 is a crystalline product.

(4) DSC data of Sample 2 (heating elevation rate: 2°C/minute)

Each of Entries A to H was placed in a first container, and 0.01 g of α-alumina (standard) was placed in a second container. The containers were placed on the sample areas of a differential scanning calorimetric thermobalance (TAS100, TG-DSC type, Rigaku Corporation), and heated at temperatures elevating from room temperature to approx. 200°C at a heating rate of 2°C/minute.

Each of Entries A to H was analyzed using a gas chromatography to determine the residual solvent content.

Further, the water content of each of Entries A to H was estimated from the data on "loss on drying" for the sodium salt.

The results are set forth in Table I.

TABLE I

(Influence of residual solvent to DSC of Sample 2)

Entries	DSC	Residual solvents (%)		
		Water	Ethyl acetate	Methanol
A	174°C	0.1	0.008	<0.005
B	171°C	0.1	<0.005	<0.005
C	173°C	0.0	<0.005	<0.005
D	170°C	0.1	0.008	<0.005
E	171°C	0.1	0.015	<0.005
F	172°C	0.1	<0.005	<0.005
G	172°C	0.1	<0.005	<0.005
H	173°C	0.2	0.006	<0.005

As is shown above (Entries A to H), the residual solvents contents are negligible in all cases, and give little influence to the DSC data.

There were no data on the residual solvent contents for Sample 1. Therefore, experiments have been newly conducted, as is described below.

(5) DSC data of Samples 1 and 2 (heating elevation rate: 2°C/minute)

Each of Entries 1-4 was placed in a first container, and 0.01 g of α-alumina (standard) was placed in a second

container. The containers were placed on the sample areas of a differential scanning calorimetric thermobalance (TAS100, TG-DSC type, Rigaku Corporation), and heated at temperatures elevating from room temperature to approx. 200°C at a heating rate of 2°C/minute.

The residual water content in each of Entries 1 to 4 was determined by the Karl-Fischer method (using CA-100/KF-100, Mitsubishi Chemical Corporation). Ethyl acetate content was determined from ^{1}H NMR spectrum of the sodium salt. Methanol content was determined using a gas chromatography.

The results are set forth in Table II.

TABLE II
(Influence of residual solvent to DSC of Sample 1)

Entry	Sample	DSC	Residual solvents (%)		
			Water	Ethyl acetate	Methanol
1	1	161°C	0.32	<0.1	-
2	1	162°C	2.35	<0.1	-
3	1	161°C	0.19	<0.1	-
4	2	173°C	0.14	<0.1	<0.005

As is shown above (Entries 1-3), there are certain differences in water contents (0.19-2.35%) among the three lots. On the other hand, the exothermic peak temperature varies only within the narrow range of 161-162°C. Apparently, no significant differences in DSC were observed though there were significant differences in water contents.

In comparison of Entry 3 with Entry 4, water contents (0.19% and 0.14%) and ethyl acetate contents are closely similar to each other. On the other hand, the exothermic peak temperatures in the DSC were distinctly different from each other (161°C and 173°C).

As is described above, the differences in the DSC data are essentially irrelevant to solvent content.

Further, the results shown in Table II show that the differences in exothermic peak temperatures in the DSC clearly distinguish the crystalline product (Sample 2: Entry 4) from the mainly amorphous product (Sample 1: Entries 1-3).

As is shown in DSC charts 1-4 (Figs. 18-21), there are clear differences in the patterns of exothermic peaks between the crystalline product (Sample 2: Entry 4) from the mainly amorphous product (Sample 1: Entries 1-3). The exothermic peak observed on the crystalline product is very sharp, while the exothermic peaks observed in Sample 1 are very broad. Therefore, from the DSC chart, Sample 1 is still considered to be a mainly amorphous product.

(6) Analysis using DSC (heating elevation rate: 5°C/minute, newly conducted experiments)

Each of Entries 1-4 was placed in a first container, and 0.01 g of α-alumina (standard) was placed in a second container. The containers were placed on the sample areas of a differential scanning calorimetric thermobalance (TAS100, TG-DSC type, Rigaku Corporation), and heated at temperatures elevating from room temperature to approx. 200°C at a heating rate of 5°C/minute.

The results are set forth in Table III. In Table III, the results at a heating elevation rate of 2°C/minute (shown in Table II) are set forth for reference.

TABLE III

(Influence of heating elevation rate to DSC)

Entry	Sample	DSC: Heating elevation rate of 2°C/minute	DSC: Heating elevation rate of 5°C/minute
1	1	161°C	161°C
2	1	162°C	160°C
3	1	161°C	160°C
4	2	173°C	181°C

As is evident from the results of Sample 1 (Entries 1-3), it is not observed that the differences in the heating elevation rates give influence exothermic peak temperatures in the DSC for Sample 1. On the other hand, the effect by the heating elevation rate is observed in the results of Sample 2 (Entry 4).

4. Conclusion

It has been confirmed that there is no significant difference between the product obtainable by Nomura et al. (Sample 1) and the product of the present invention (Sample 2) as far as the IR spectrum is concerned.

However, there are the following differences between the product obtainable by Nomura et al. (Sample 1) and the product of the present invention (Sample 2).

The mainly amorphous product obtainable in Example 48 of Nomura et al. (Sample 1) is clearly different from a crystalline product of the present invention (Sample

2), as is shown in the microscopic pictures and the powder X-ray diffraction data.

As is shown in the results of DSC, the mainly amorphous product obtainable in Example 48 of Nomura et al. (Sample 1) is outside the scope (DSC peak: 170 to 175°C) of claim 1 according to the present invention.

Apparently, the differences in the DSC data cannot be attributed to solvent content.

The undersigned declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date March 4, 2009

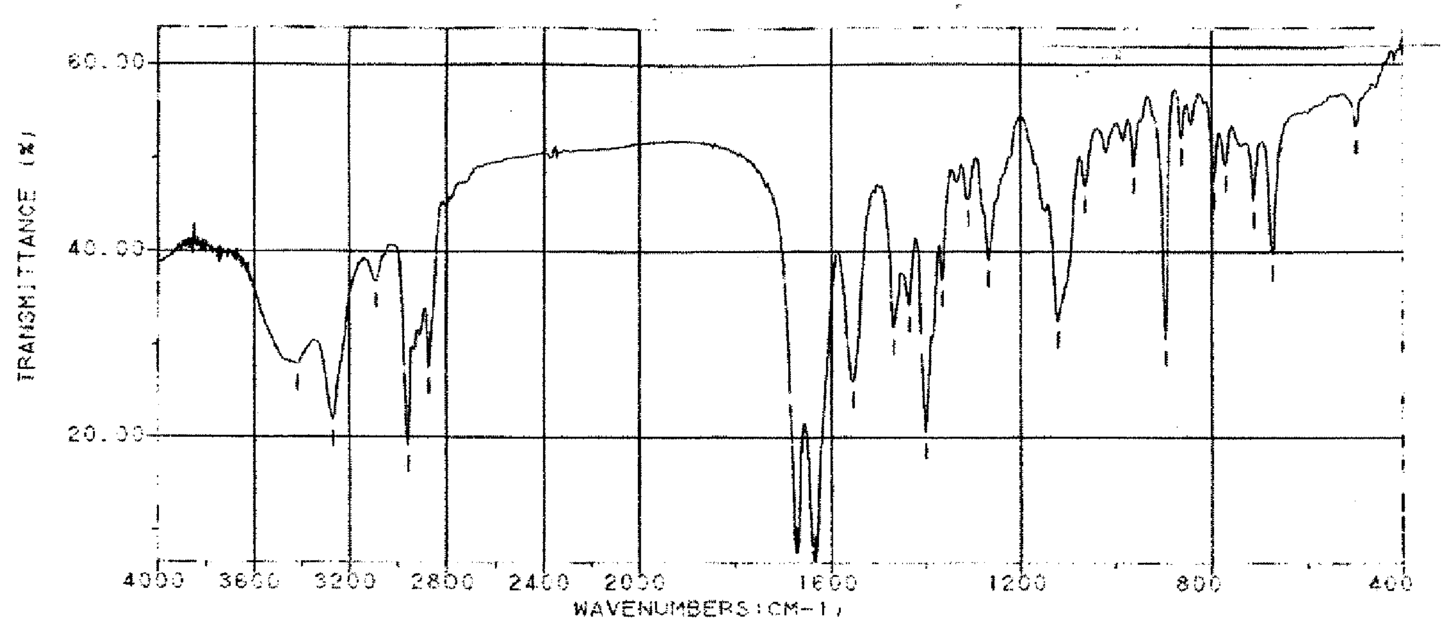
Toshihiro Takahashi

Toshihiro TAKAHASHI

Fig. 1

Instrument: JIR-6500 (JEOL)

(IR spectrum 1)



RESOL	:4cm-1	3417.28	27.83	1402.01	20.50	769.47	49.22
SCANS	:10	3266.86	21.82	1367.30	36.93	711.61	45.41
AMPGAIN	:x2	3089.44	36.74	1311.37	45.49	673.04	39.72
P.INT	:2cm-1	2956.38	19.05	1268.95	39.12	497.55	53.30
BEAM	:dual	2871.52	27.51	1120.45	32.51		
S.SPEED	:TGS	1672.00	7.57	1064.53	47.01		
S.NUMBER	:1	1633.43	6.58	962.32	49.02		
M.DATE	:2/26/98	1554.36	26.00	894.82	30.56		
		1469.51	31.68	862.04	52.09		
		1436.73	34.14	794.54	47.33		

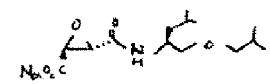


Fig. 2

Instrument: HITACHI, Type 260-50

(IR spectrum 2)

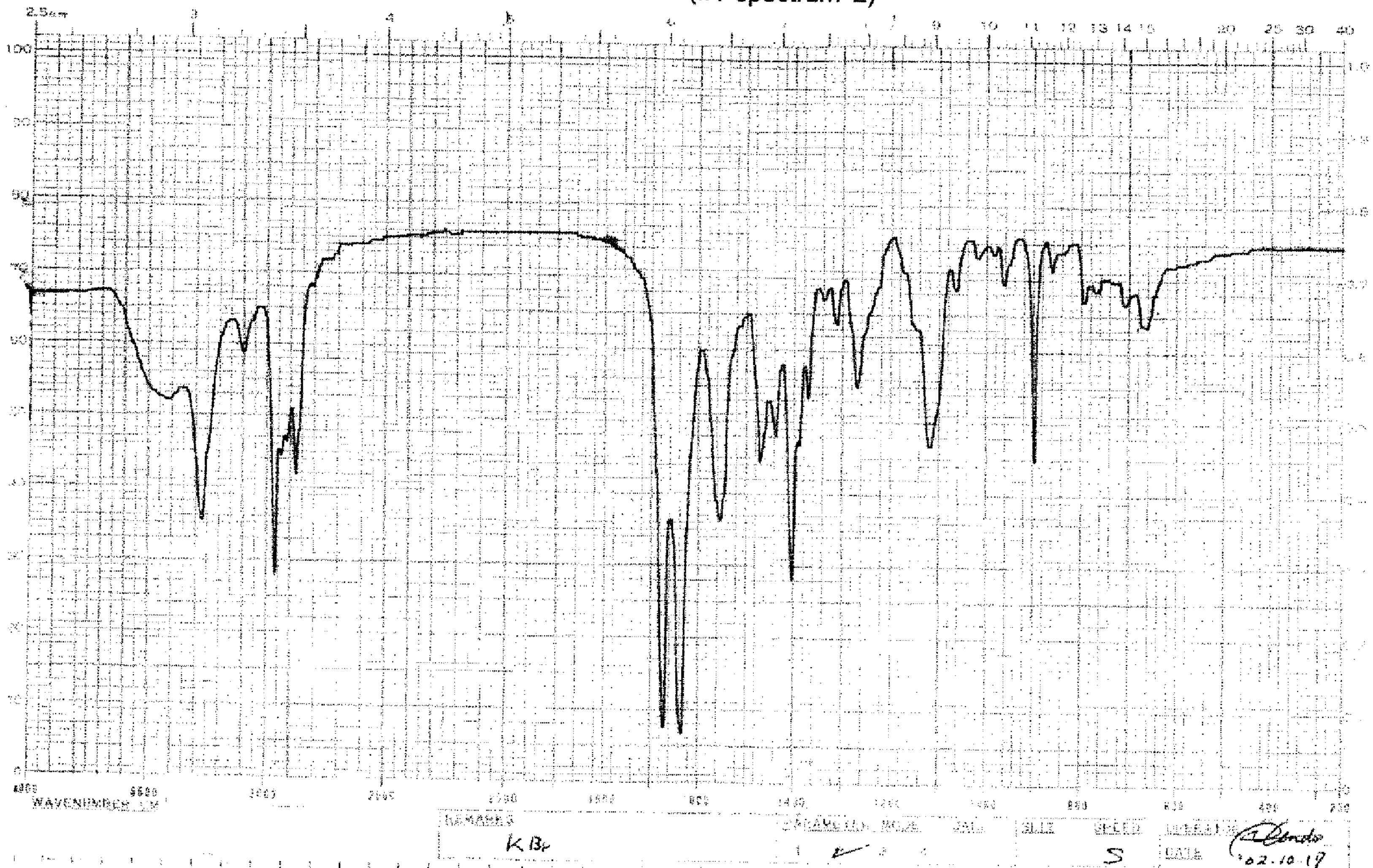
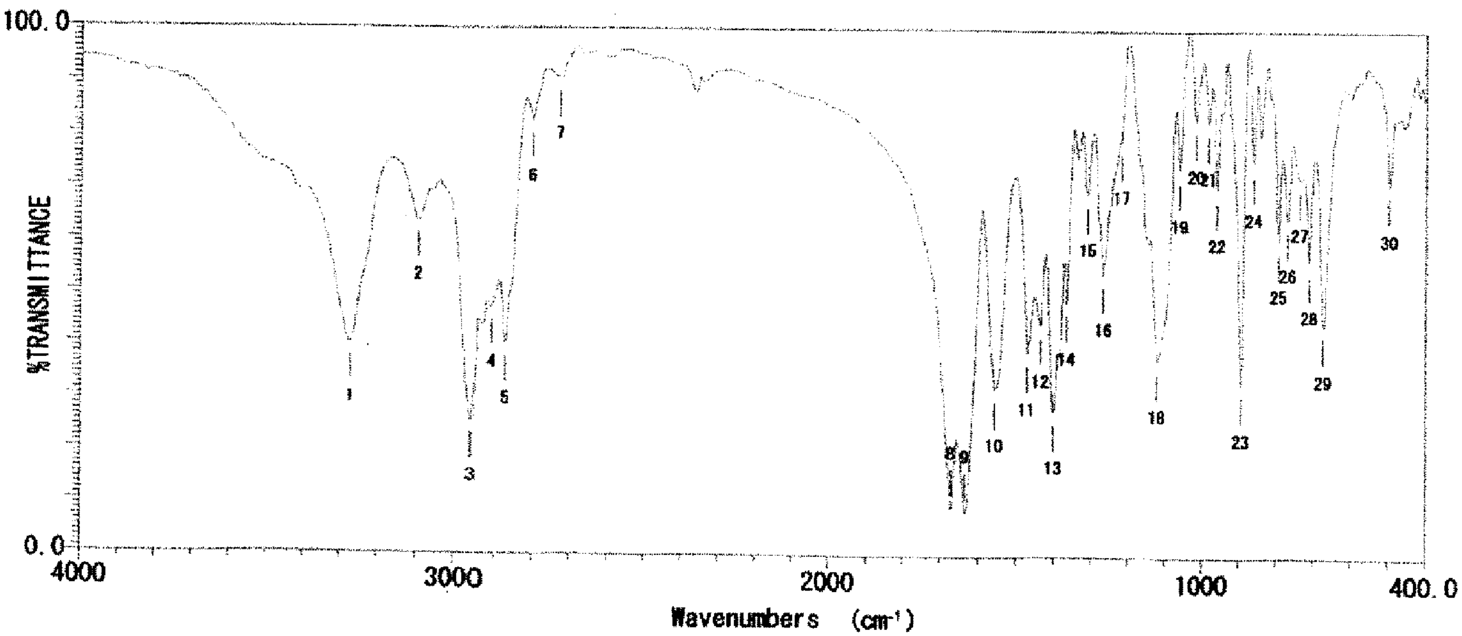


Fig. 3

(IR spectrum 3)

Instrument: Fourier Transform Infrared Spectroscopy, FT-720, HORIBA

HORIBA FT-IR for Windows(TM) Ver.4.07
FTIR system for Windows



Date: February 23, 2009
Resolving power: 4 cm^{-1}
Scans: 10 times
Gain: 1

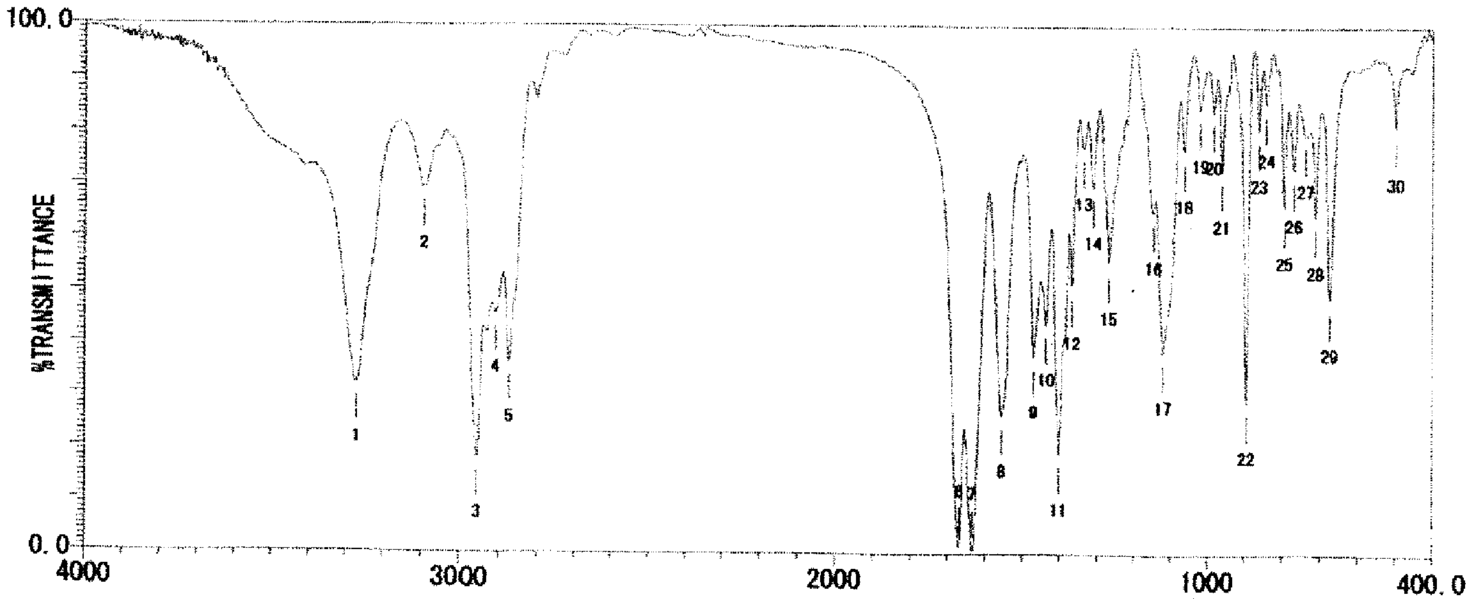
Peak Number	Wave-number (cm^{-1})	Trans-mittance (%)	Peak Number	Wave-number (cm^{-1})	Trans-mittance (%)	Peak Number	Wave-number (cm^{-1})	Trans mittance (%)
01	3270.68	40.1400	11	1471.42	38.6463	21	985.447	82.9181
02	3091.33	63.5697	12	1436.71	44.0377	22	962.305	70.0990
03	2958.27	25.3244	13	1402.00	27.5149	23	894.809	32.8891
04	2908.13	48.9810	14	1367.28	48.3406	24	862.025	75.0822
05	2871.49	40.0642	15	1311.36	69.1760	25	794.528	60.4704
06	2800.13	82.6007	16	1268.93	53.9296	26	769.458	64.4890
07	2726.85	90.6355	17	1220.72	79.2466	27	738.603	72.2449
08	1671.98	9.15169	18	1122.37	37.3099	28	711.604	56.4173
09	1635.34	8.46348	19	1064.51	73.8446	29	673.035	44.1526
10	1558.20	31.7561	20	1020.16	83.2255	30	497.544	71.0679

Fig. 4

(IR spectrum 4)

Instrument: Fourier Transform Infrared Spectroscopy, FT-720, HORIBA

HORIBA FT-IR for Windows(TM) Ver.4.07
FTIR system for Windows



Date: October 22, 2008
Resolving power: 4 cm^{-1}
Scans: 10 times
Gain: 1

Peak Number	Wave-number (cm^{-1})	Trans-mittance (%)	Peak Number	Wave-number (cm^{-1})	Trans-mittance (%)	Peak Number	Wave-number (cm^{-1})	Trans mittance (%)
01	3268.75	32.1856	11	1402.00	18.8946	21	962.305	73.0665
02	3091.33	69.2354	12	1367.28	50.8868	22	894.809	28.9341
03	2958.27	18.0563	13	1336.43	77.3188	23	862.025	80.8208
04	2908.13	45.7263	14	1311.36	69.8816	24	842.740	85.6798
05	2871.49	36.1716	15	1268.93	55.4929	25	794.528	66.1483
06	1670.05	1.36588	16	1147.44	65.1814	26	769.458	73.3030
07	1635.34	0.88766	17	1120.44	38.3248	27	738.603	79.8799
08	1556.27	26.3096	18	1064.51	76.8471	28	711.604	64.3122
09	1469.49	37.5003	19	1020.16	84.5860	29	673.035	48.6634
10	1436.71	43.7098	20	983.518	84.3542	30	497.544	81.1366

Fig. 5

(IR spectrum 5)

Instrument: Fourier Transform Infrared Spectroscopy, FT-720, HORIBA

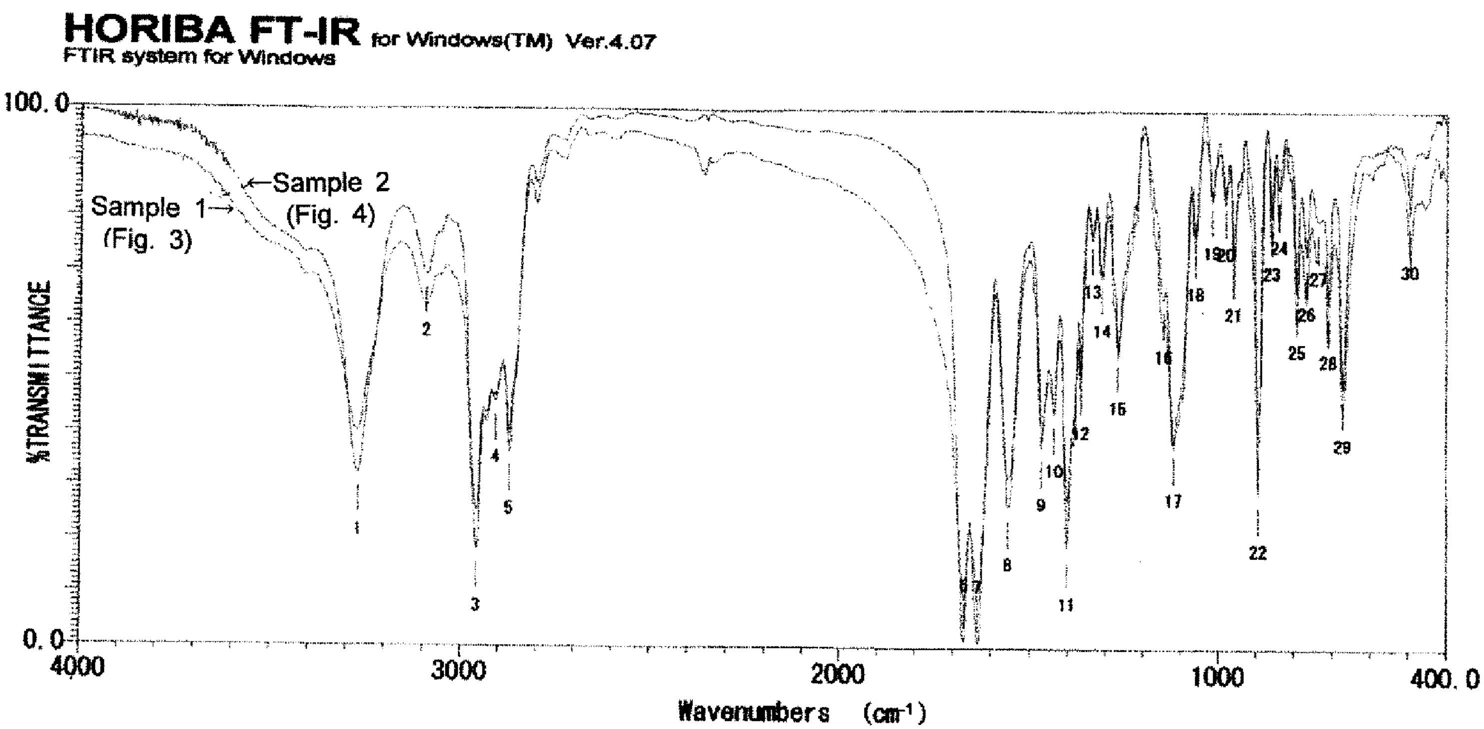


FIG. 6

(Polarizing microscopic picture 1)

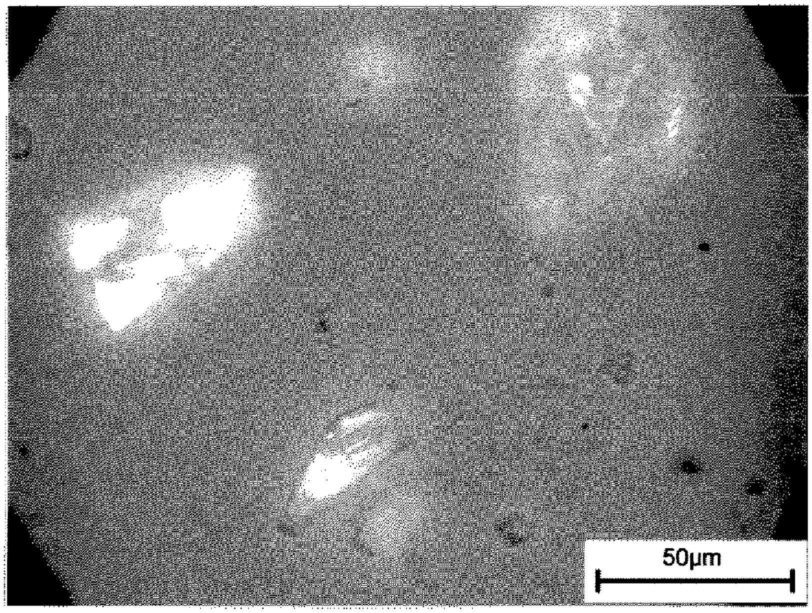


FIG. 7

(Polarizing microscopic picture 2)

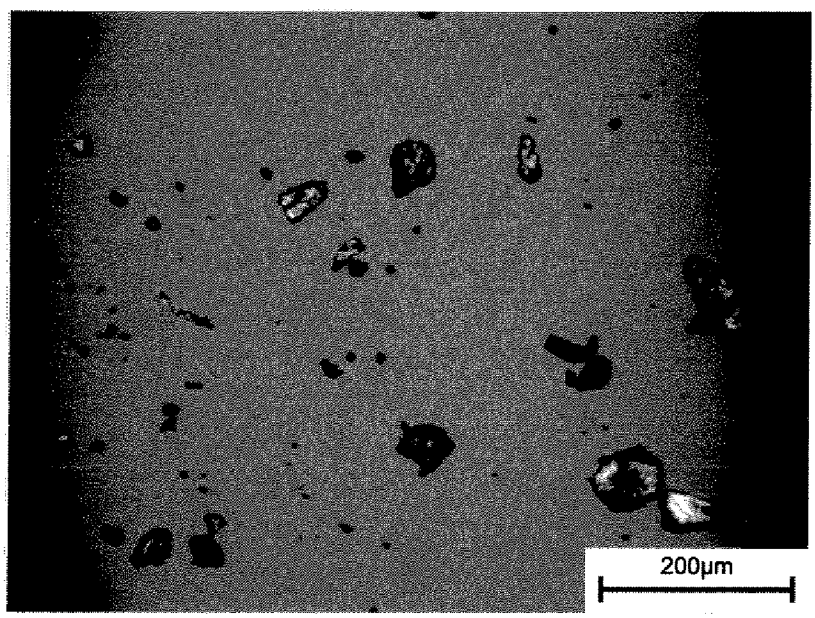


FIG. 8

(Polarizing microscopic picture 3)

FIG. 9

(Polarizing microscopic picture 4)

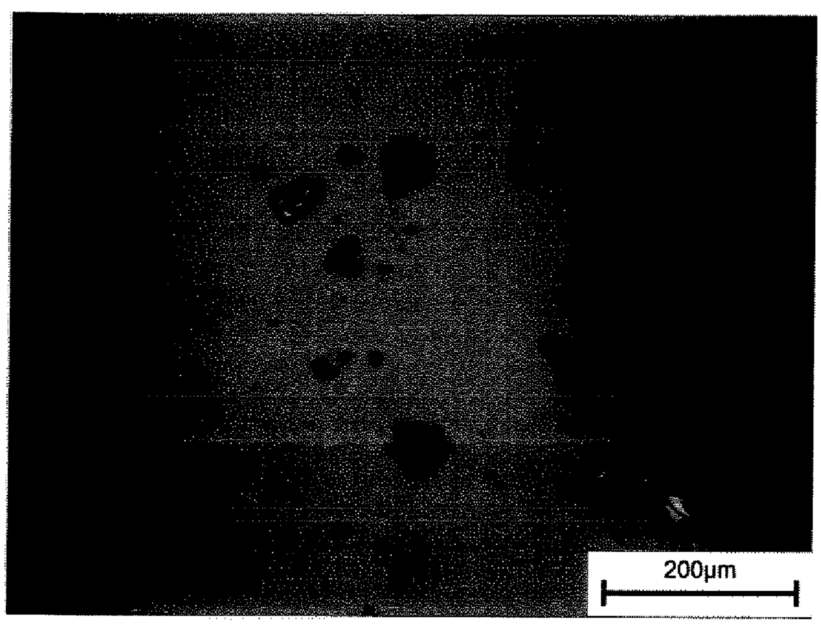


FIG. 10

(Polarizing microscopic picture 5)

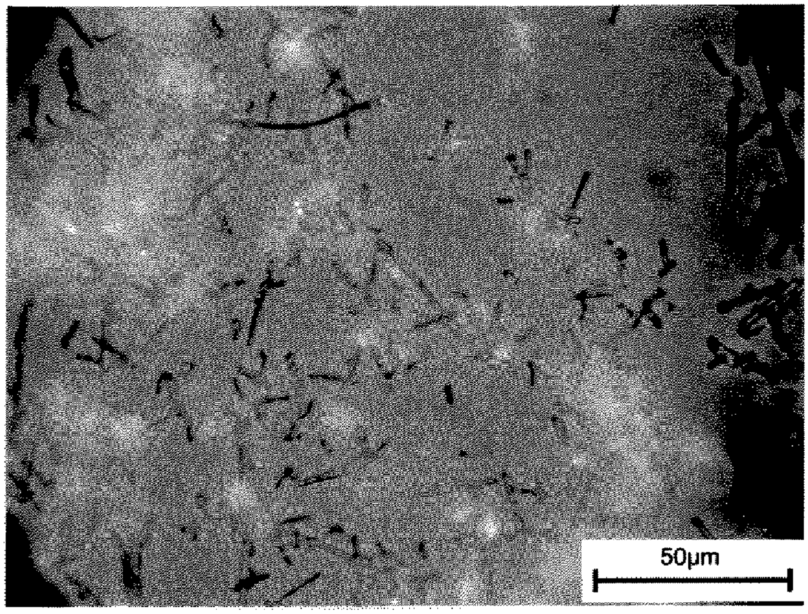


FIG. 11

(Polarizing microscopic picture 6)

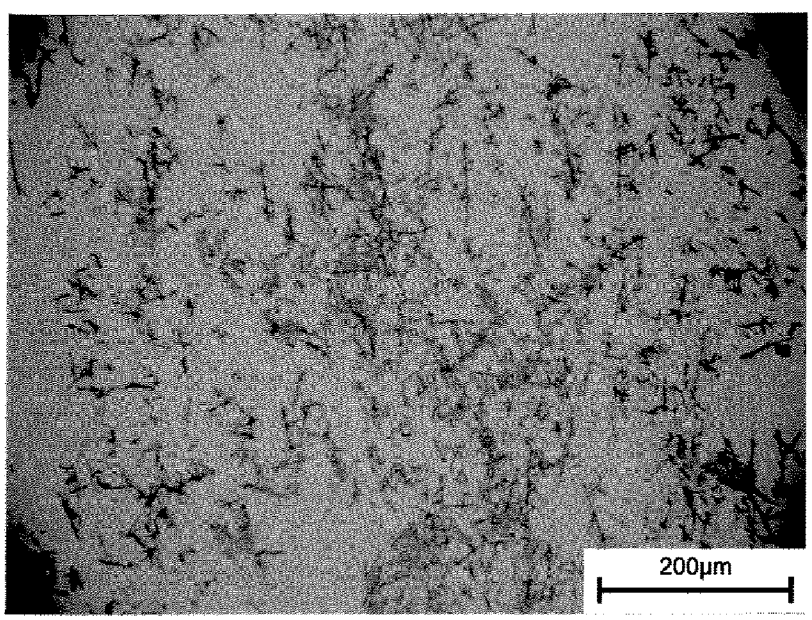


FIG. 12

(Polarizing microscopic picture 7)

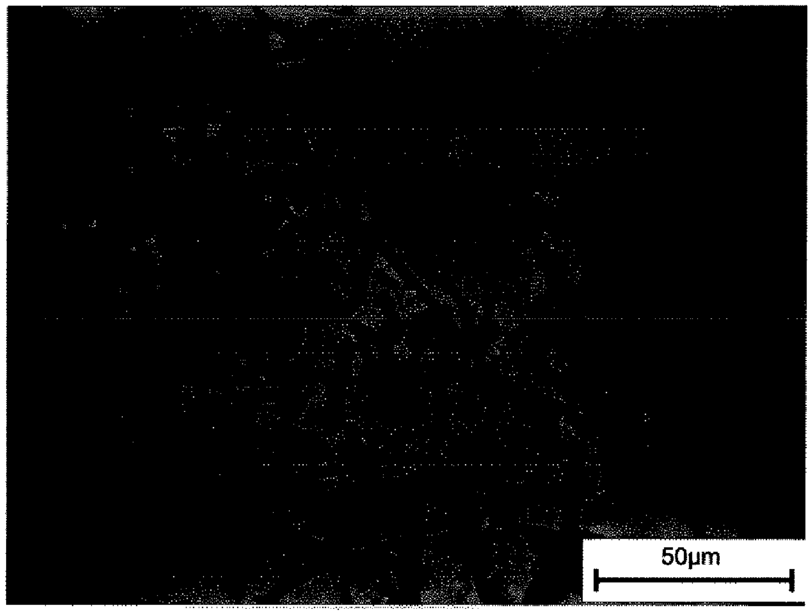


FIG. 13

(Polarizing microscopic picture 8)

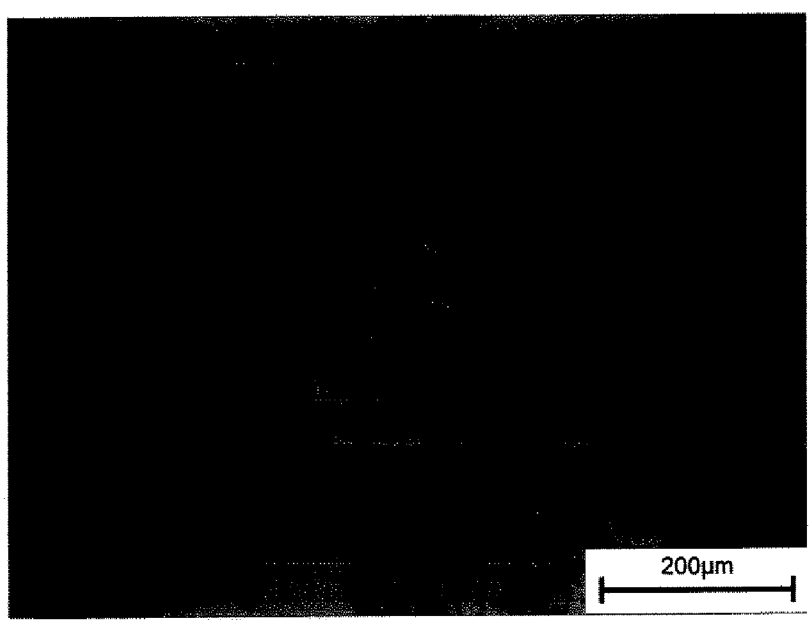


FIG. 14

(Electron microscopic picture 1)

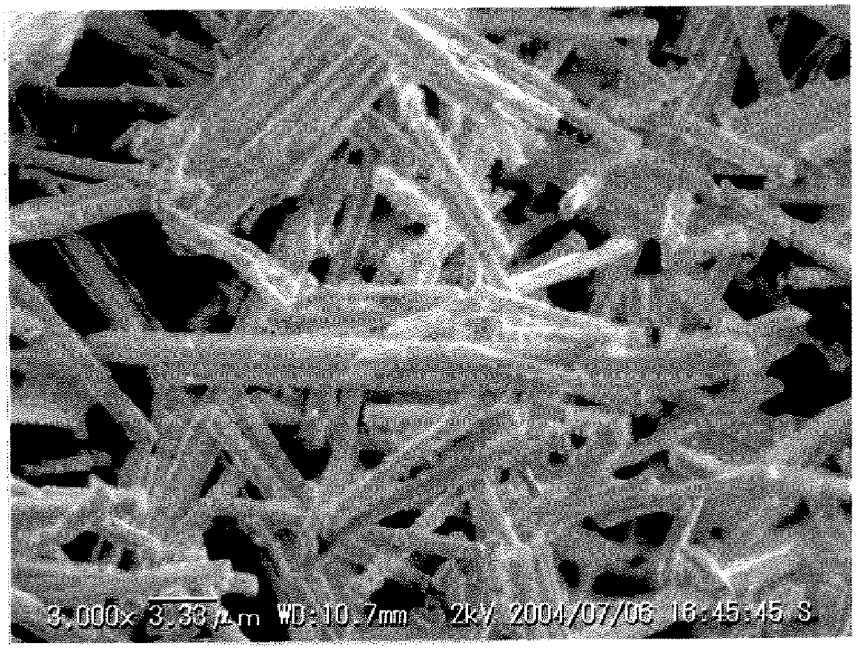


FIG. 15

(Electron microscopic picture 2)

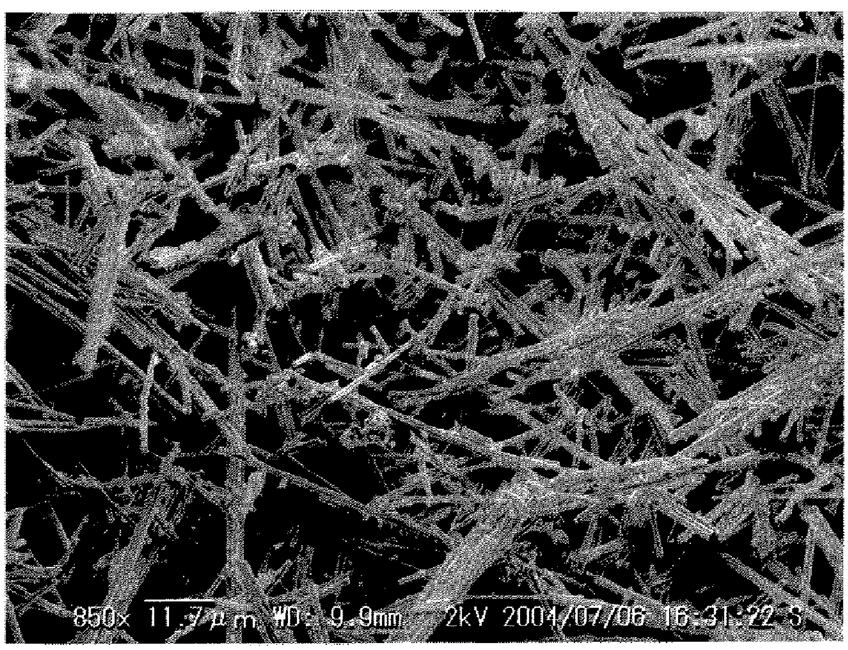


Fig. 16

(PXRD 1)

Sample: Na salt obtained by '908 patent method (Conventional method)

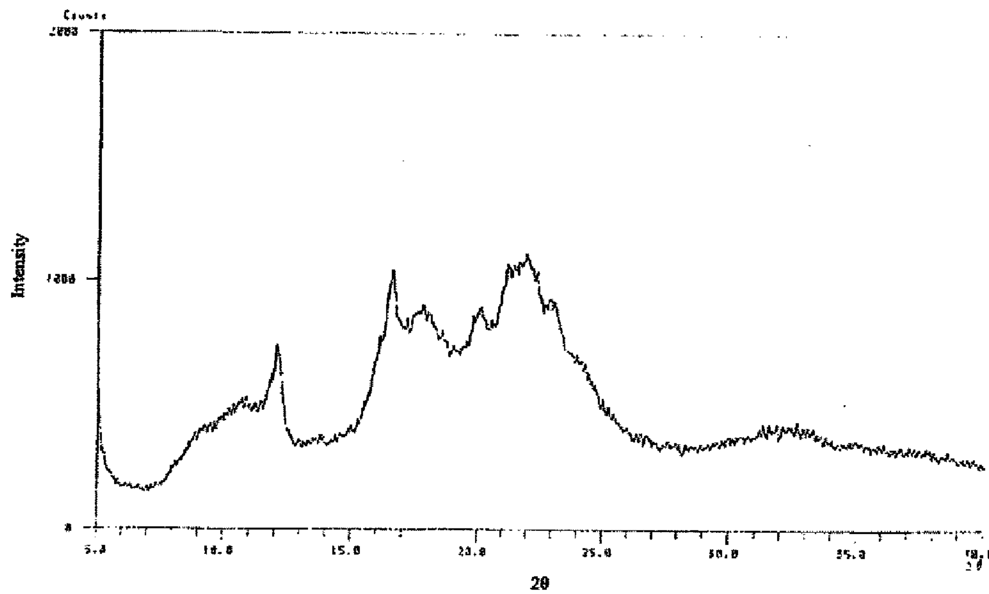


Fig. 17

(PXRD 2)

Sample: Na salt obtained by '826 application method

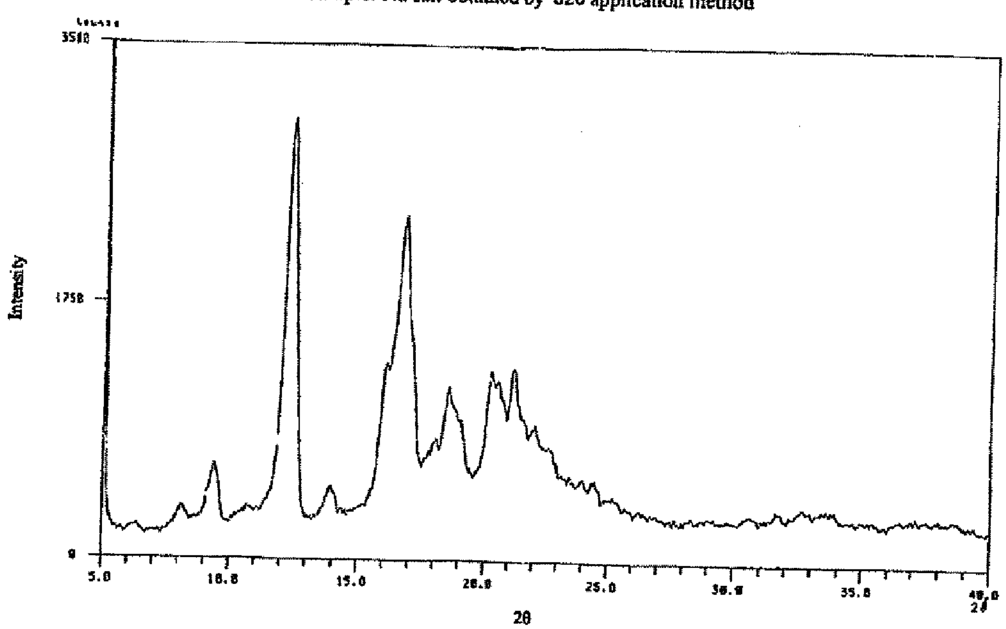


Fig. 18

(DSC chart 1)

Thermal Analysis

Sample: Na salt described in Table II, entry 1

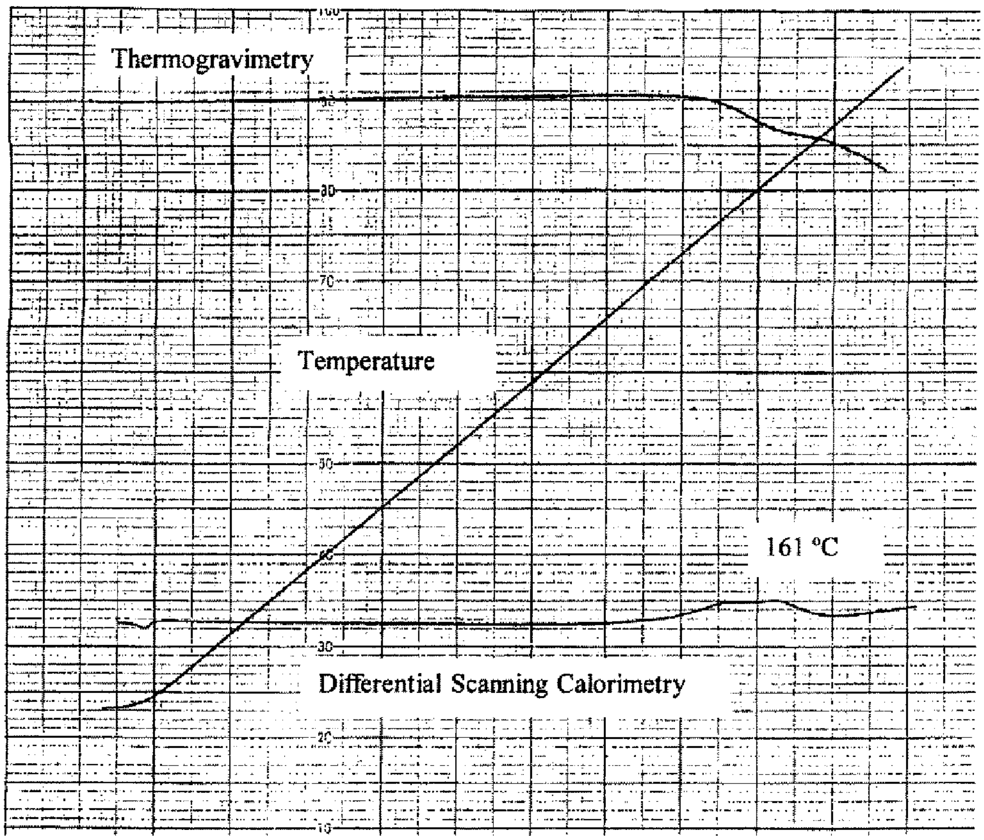


Fig. 19

(DSC chart 2)

Thermal Analysis

Sample: Na salt described in Table II, entry 2

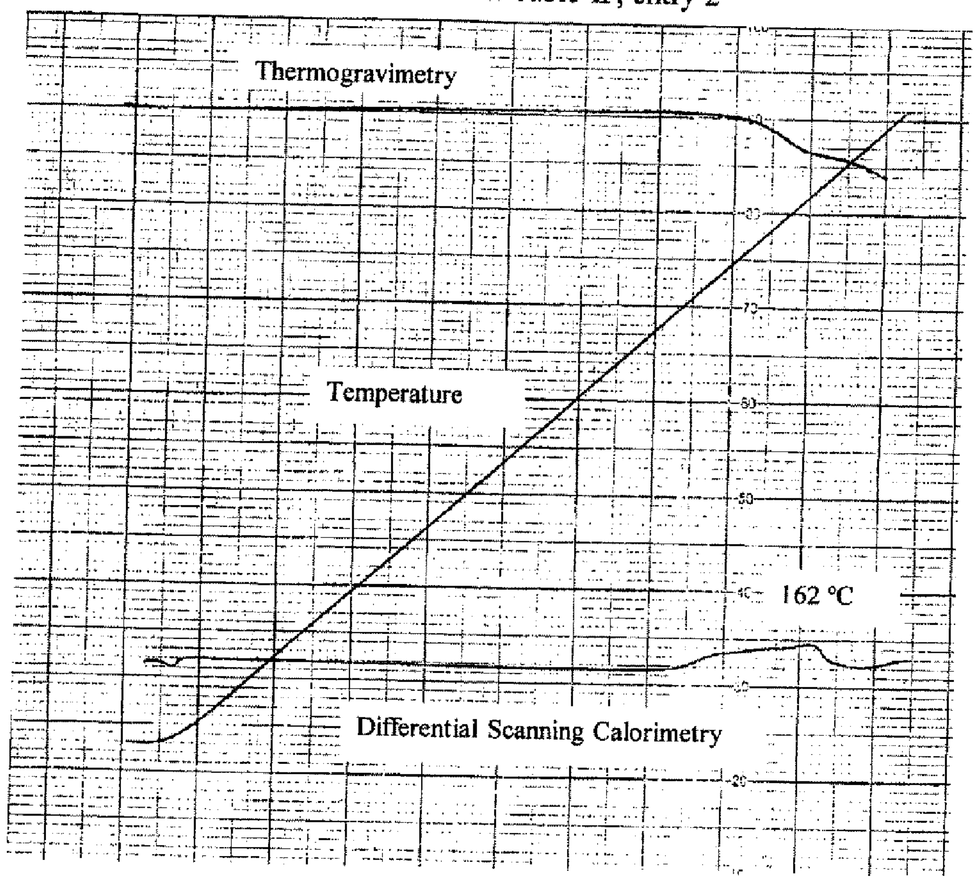


Fig. 20

(DSC chart 3)

Thermal Analysis

Sample: Na salt described in Table II, entry 3

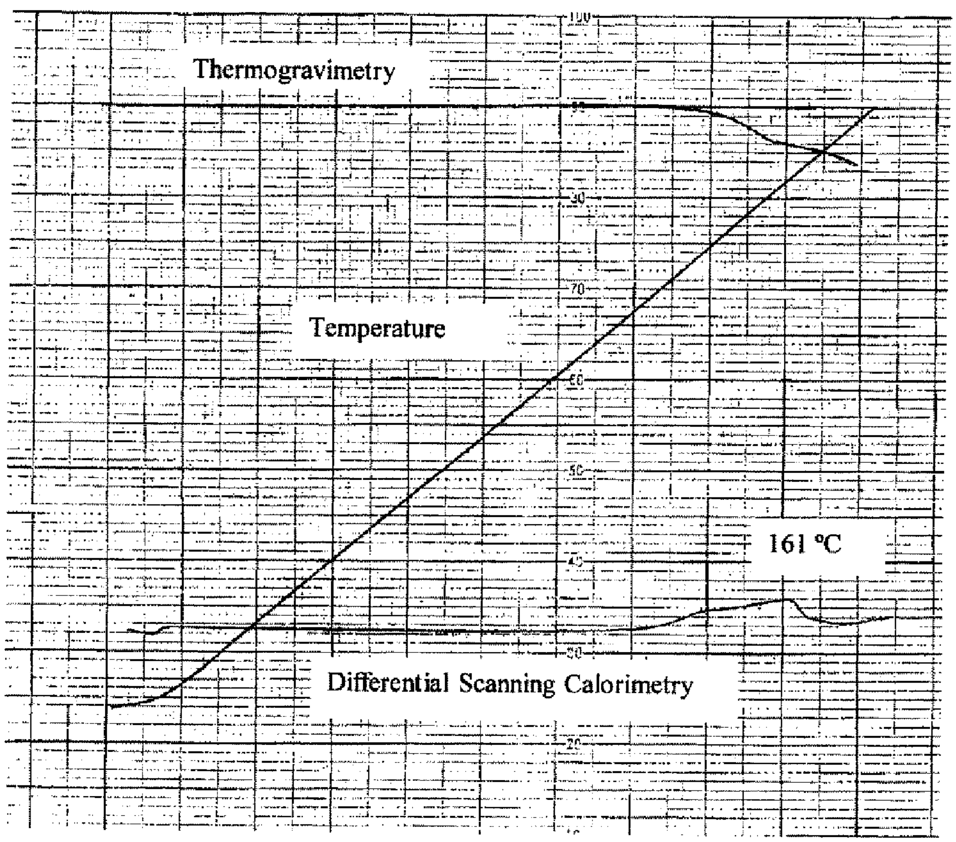


Fig. 21

(DSC chart 4)

Thermal Analysis

Sample: Na salt described in Table II , entry 4